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09/731,830	12/08/2000	Junji Hamare	200488US SCONT	[illegible]

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EXAMINER	
KAM, CHIH MIN	
ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 02/11/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/731,830	Applicant(s) HAMURO ET AL.	
	Examiner Chih-Min Kam	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 November 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,11 and 20-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,11 and 20-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *09/334,647* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

1. Claims 1-3, 11 and 20-29 are pending.

Applicants' amendment filed on November 23, 2001 (Paper No. 7) has been entered and applicant's response has been fully considered. Claims 1, 2 and 11 have been amended, and new claims 20-29 have been added.

Rejection Withdrawn

Claim Rejections – Obviousness Type Double Patenting

2. The previous rejection of claims 1-3 and 11 on obviousness type double patenting, is withdrawn in view of applicants' submission of terminal disclaimer (Paper No. 8).

Claim Rejections - 35 USC § 102(b)

3. The previous rejection of claim 1 under 35 U.S.C.102(b) as being anticipated by Anderson *et al.* (U. S. Patent 5,476,966), is withdrawn in view of applicants' amendment to the claims and applicants' response at pages 4-5 in Paper No. 7.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-3, 11 and 20-29 are rejected because the specification, while being enabling for a method of treating cachectic condition caused by cancers.....or autoimmune inflammatory diseases, comprising administering to a patient an effective amount of composition comprising a cystine compound of formula (I) which reduces the content of reductive glutathione in

macrophages, suppresses cellular responses, increases IL-6 production by macrophages, and decreases IL-12 and NO production by macrophages, does not reasonably provide enablement for a method of treating cachectic condition caused by the recited diseases, or, for a method of treating diabetes, gastrointestinal inflammatory diseases, chronic rheumatoid arthritis, hepatitis, hepatic cirrhosis, hypersensitive interstitial pneumonia, pulmonary fibrosis or autoimmune inflammatory diseases comprising administering to a patient an effective amount of composition comprising a substance which reduces the content of reductive glutathione in macrophages suppresses cellular responses, increases IL-6 production by macrophages, and decreases IL-12 and NO production by macrophages. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-3, 11, 28 and 29 encompass a method of treating cachectic condition caused by cancers.....or autoimmune inflammatory diseases, and claims 20-27 encompass a method of treating diabetes, gastrointestinal inflammatory diseases, chronic rheumatoid arthritis, hepatitis, hepatic cirrhosis, hypersensitive interstitial pneumonia, pulmonary fibrosis or autoimmune inflammatory diseases, comprising administering to a patient an effective amount of composition comprising a substance which reduces the content of reductive glutathione in macrophages, suppresses cellular responses, increases IL-6 production by macrophages, and decreases IL-12 and NO production by macrophages. The specification, however, only discloses cursory conclusions (see page 4, line 19-22; page 14, line 27-page 15, line 1; page 1, lines 5-15) without data supporting the findings, which states that a method of suppressing immune responses such as treating cachectic condition caused by cancers.....or autoimmune inflammatory diseases,

comprising administering to a patient an effective amount of composition comprising a substance which reduces the content of reductive glutathione in macrophages. There are no indicia that the present application enables the full scope in view of treating cachectic condition caused by the recited diseases and of treating these diseases as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is encompassed. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breath of the claims, the absence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breath of the claims:

The breath of the claims is broad and encompasses an unspecified amount of variants regarding the substance which reduces the content of reductive glutathione in macrophages and is used for treating cachectic condition caused by the recited diseases and for treating the recited diseases, and the treating conditions for treating recited diseases, which are not adequately described or demonstrated in the specification.

(2). The absence of working examples:

There are no working examples indicating the claimed methods in association with the variants except for cystine compounds.

(3). The state of the prior art and relative skill of those in the art:

The general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the identities of the substance and the treating conditions for treating various recited diseases to be considered enabling for variants.

(4). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method of treating cachectic condition caused by various diseases (claims 1-3, 11, 28 and 29), and a method of treating diabetes, gastrointestinal inflammatory diseases, chronic rheumatoid arthritis, hepatitis, hepatic cirrhosis, hypersensitive interstitial pneumonia, pulmonary fibrosis or autoimmune inflammatory diseases (claims 20-27), comprising administering to a patient a substance which reduces the content of reductive glutathione in macrophages. The specification indicates cystine compounds of formula (I) are used to treat cachectic condition caused by various recited diseases and the effects of the cystine compounds on the cachectic condition caused by inflammatory bowl disease, adjuvant-induced arthritis and dibetes mellitus in animal models have been shown (pages 9-10; Examples). However, the specification fails to identify any substance other than cystine compounds of formula (I) which reduce the content of reductive glutathione in macrophages and to provide any example of using the substance for treating cachectic condition caused by various recited diseases. Moreover, the specification has not shown the treating conditions for various recited diseases such as diabetes, gastrointestinal inflammatory diseases, chronic rheumatoid arthritis, hepatitis, hepatic cirrhosis, hypersensitive interstitial pneumonia, pulmonary fibrosis or autoimmune inflammatory diseases using the substance. There are no working examples of

these methods in the specification. Furthermore, the specification does not provide any specific guidance as to how to treat the diseases described above, for example, the dosage, the time, and the frequency of the treatment as well as how the effect of the substance being monitored. Since the specification fails to provide sufficient guidance on the identity of the substance other than cystine compounds and the treating conditions for various recited diseases, it is necessary to have additional guidance and to carry out further experimentation to assess the effect of the substance which is used for the treatment.

(5). Predictability or unpredictability of the art:

The claims encompass treating cachectic condition caused by various recited diseases and treating diseases using the substance which reduces the content of reductive glutathione in macrophages, however, the substance and the treating conditions for the diseases are not sufficiently described in the specification, the invention is highly unpredictable regarding the outcome of the treatment. For example, $(NAC\text{-}OMe)_2$ and $(NAC)_2$ both are cystine compounds and have similar effects on inhibiting production of NO, IL-6 and IL-12 from macrophages (Table 1), however, the $(NAC\text{-}OMe)_2$ is effective in reducing swelling in the animal model of adjuvant-induced arthritis but $(NAC)_2$ is not (Table 3).

(6). Nature of the Invention

Scope of the claims includes treating cachectic condition caused by various recited diseases and treating recited diseases using the substance which reduces the content of reductive glutathione in macrophages, but the specification does not show what compounds besides cystine compounds are used and how these various recited diseases are being treated using the substance. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed variants, and the guidance and the teaching in the specification is limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the outcome of the treatment using the substance as indicated by the claim.

In response, applicant indicates although cystine derivatives are used as materials to reduce the content of reductive glutathione in macrophage, the specification provides sufficient basis that any substance which reduces the content of reductive glutathione in macrophage are operative in the same manner as cystine derivatives. The argument is not persuisive because compounds with different structures would have different effect in treating diseases, it is unpredictable regarding the outcome of the treatment. For example, $(NAC\text{-}OMe)_2$ and $(NAC)_2$ both are cystine derivatives and have similar effects on inhibiting production of NO, IL-6 and IL-12 from macrophages (see Table 1), however, $(NAC\text{-}OMe)_2$ is effective in reducing swelling in the animal model of adjuvant-induced arthritis but $(NAC)_2$ is not (see Table 3). Therefore, it is necessary to to have additional guidance on the substance and the treating conditions for the recited diseases and to carry out further experimentation to assess the outcome of the treatment using the substance.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-3, 11 and 20-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3, 11 and 20-29 are indefinite because the claims lack essential steps in the method of treating cachectic condition caused by various recited diseases and of treating diseases using the substance which reduces the content of reductive glutathione in macrophages. The omitted steps are: the method of administration and a step whereby the outcome and the time for effective treatment can be determined. Claims 2-3, 11 and 20-29 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

6. Claim 3 is indefinite because of the use of the term "cystine derivative". The term "cystine derivative" renders the claim indefinite, it is not clear what kind of cystine compound is intended as compared to the parent compound, cystine.

7. Claim 11 is indefinite because of the use of the terms "said substance is a conjugate of a cytotoxic DNA alkylating agent and glutathone" and "one which shows cytotoxicity after being incorporated into macrophage as a precursor". The terms "said substance is a conjugate of a cytotoxic DNA alkylating agent and glutathone" and "one which shows cytotoxicity after being incorporated into macrophage as a precursor" render the claim indefinite, it is unclear in the claim how a substance, which is a conjugate of a cytotoxic DNA alkylating agent and glutathone, can also reduce the content of reductive glutathione in macrophage to meet the limitation of claim 1; it is also unclear what compound is as to one which shows cytotoxicity after being incorporated into macrophage as a precursor, and how a compound which has cytotoxicity can

reduce the content of reductive glutathione in macrophage to meet the limitation of claim 1. See also claims 29.

8. Claim 28 is indefinite because a cytotoxic DNA alkylating agent, which is conjugated with glutathione, is deconjugated by glutathione S-transferase and can remove the reductive macrophage by killing the macrophage as stated in the specification (see page 9, lines12-15), it is unclear how a cytotoxic DNA alkylating agent can reduce the content of reductive glutathione in macrophage to meet the limitation of claim 1.

Conclusion

9. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, Ph. D. can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

Karen Cochrane Carlson PhD
KAREN COCHRANE CARLSON PH.D
PRIMARY EXAMINER

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January 31, 2002